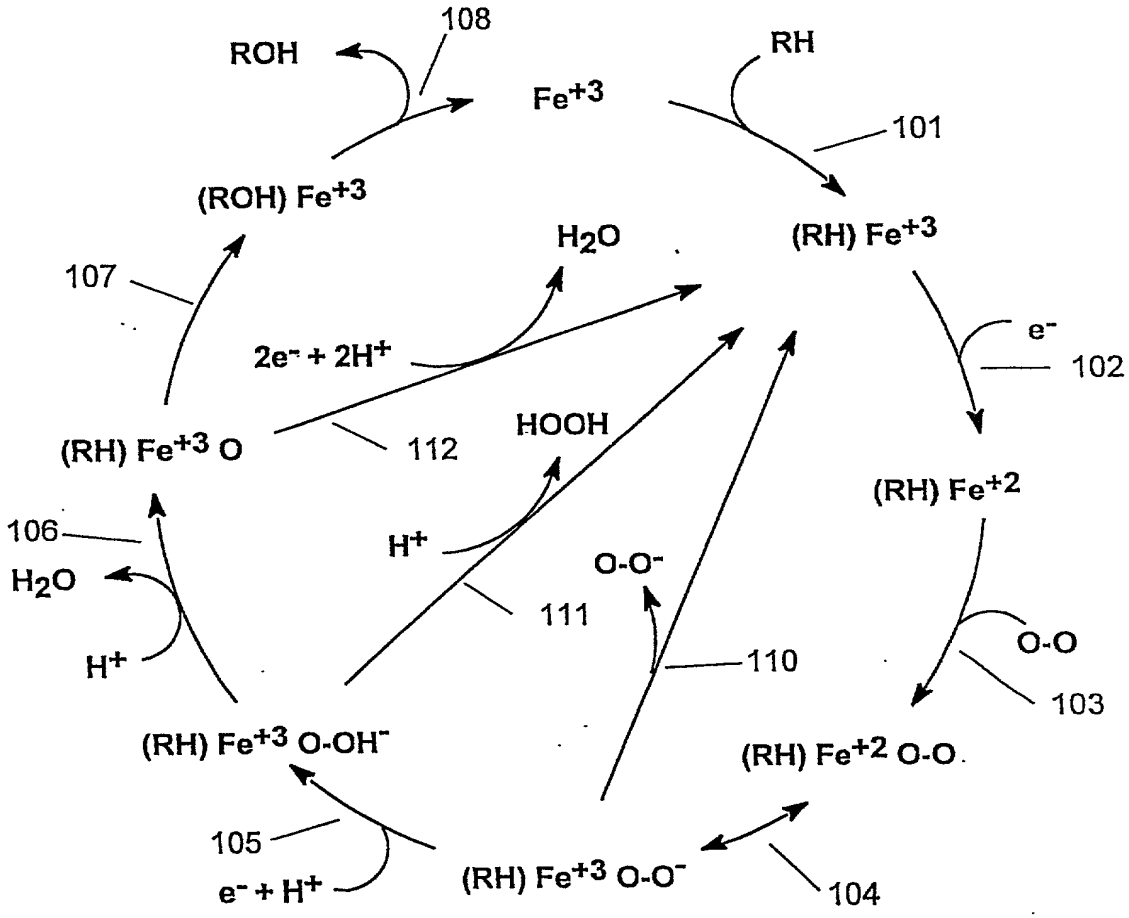

ROH
108
Fe+3
RH
101
(ROH) Fe+3
H2O
(RH) Fe+3
107
2e- + 2H+
e-
102
(RH) Fe+3 O
112
HOOH
(RH) Fe+2
106
H+
O-O-
H2O
111
O-O
H+
110
103
(RH) Fe+3 O-OH-
(RH) Fe+2 O-O
105
e- + H+
(RH) Fe+3 O-O-
104

FIGURE 1

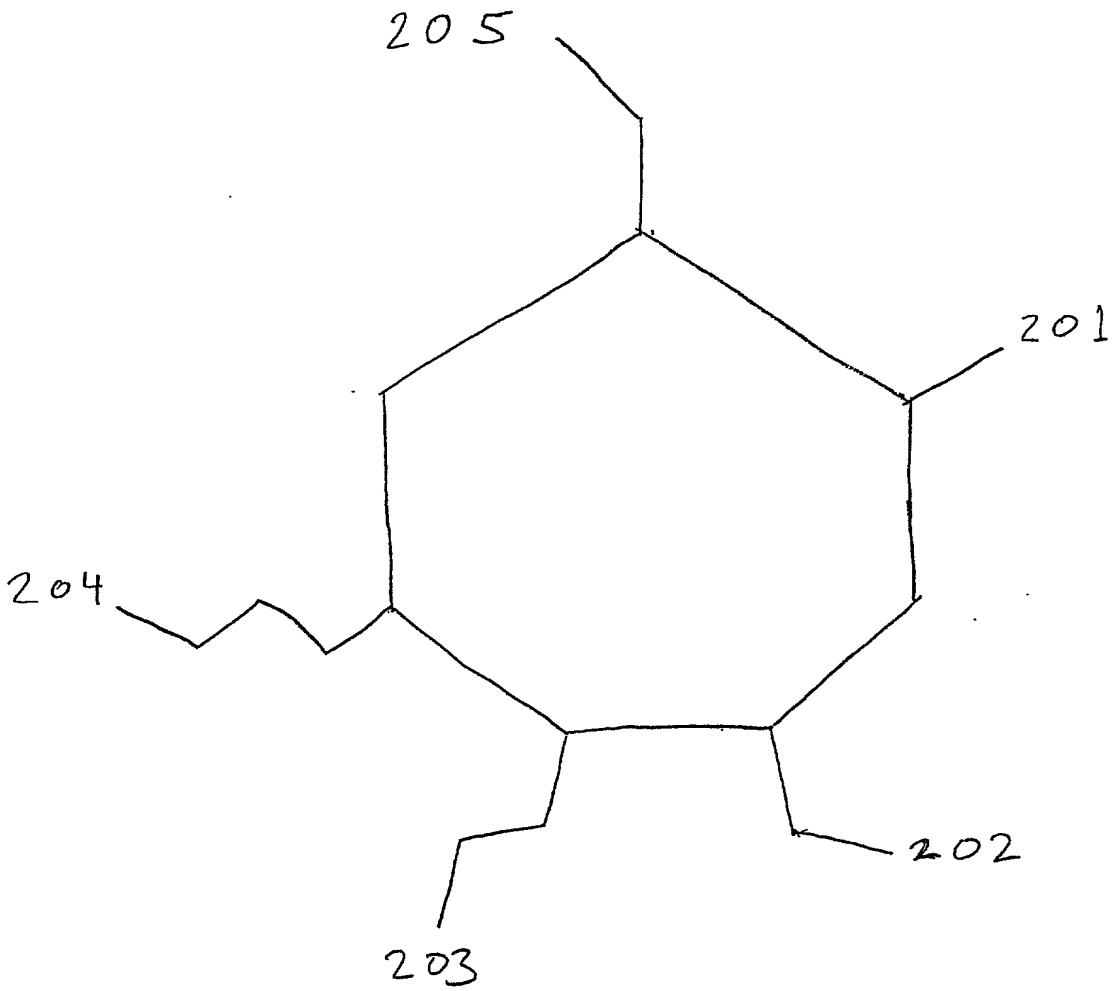


Figure 2

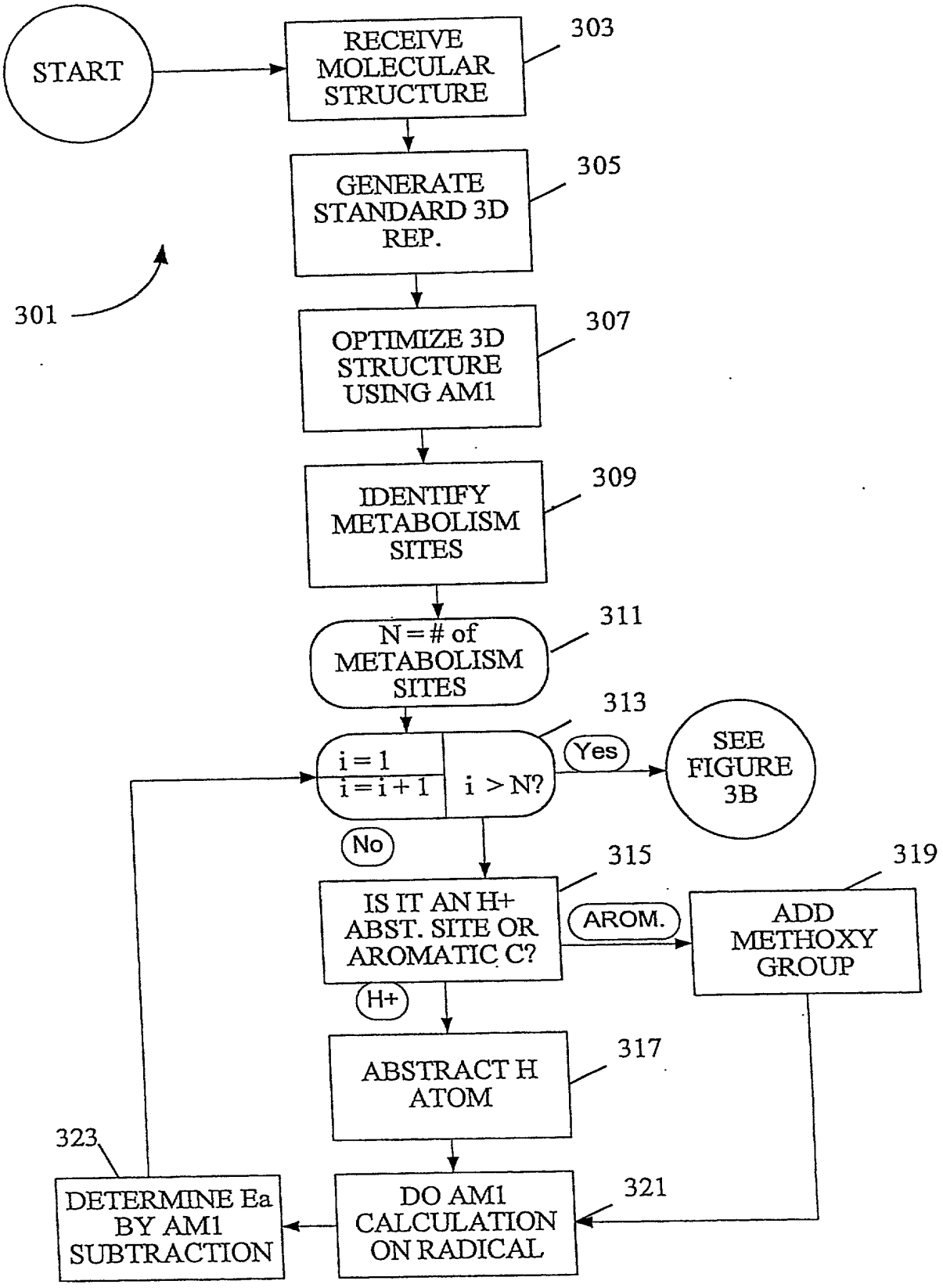

START
RECEIVE MOLECULAR STRUCTURE
303
GENERATE STANDARD 3D REP.
305
301
OPTIMIZE 3D STRUCTURE USING AM1
307
IDENTIFY METABOLISM SITES
309
N = # of METABOLISM SITES
311
313
i = 1
i = i + 1
i > N?
Yes
SEE FIGURE 3B
No
315
IS IT AN H+ ABST. SITE OR AROMATIC C?
AROM.
319
ADD METHOXY GROUP
H+
ABSTRACT H ATOM
317
323
DETERMINE Ea BY AM1 SUBTRACTION
DO AM1 CALCULATION ON RADICAL
321

FIGURE 3A

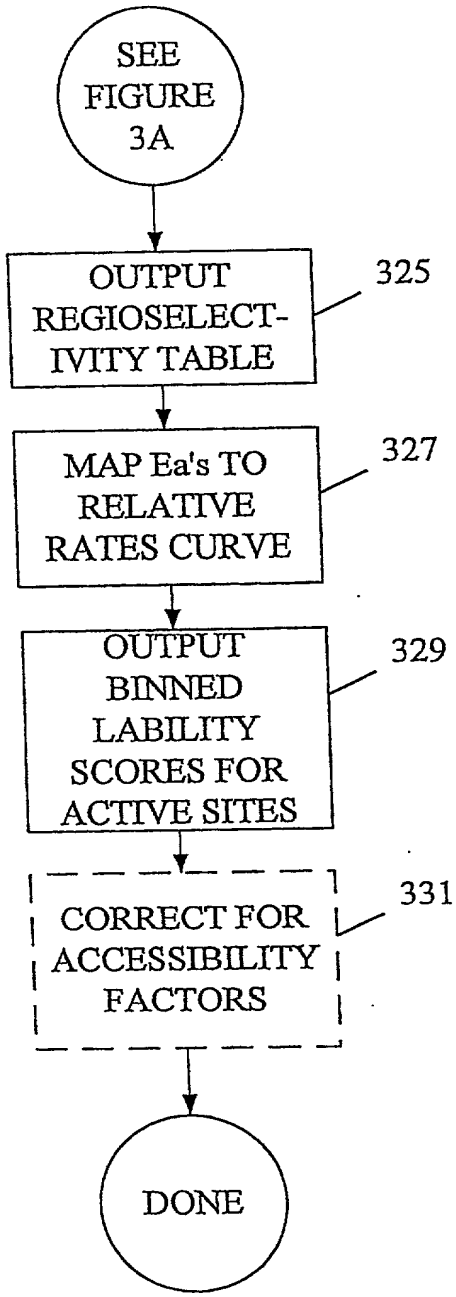

SEE FIGURE 3A
OUTPUT REGIOSELECT-IVITY TABLE
325
MAP Ea's TO RELATIVE RATES CURVE
327
OUTPUT BINNED LABILITY SCORES FOR ACTIVE SITES
329
CORRECT FOR ACCESSIBILITY FACTORS
331
DONE

FIGURE 3B

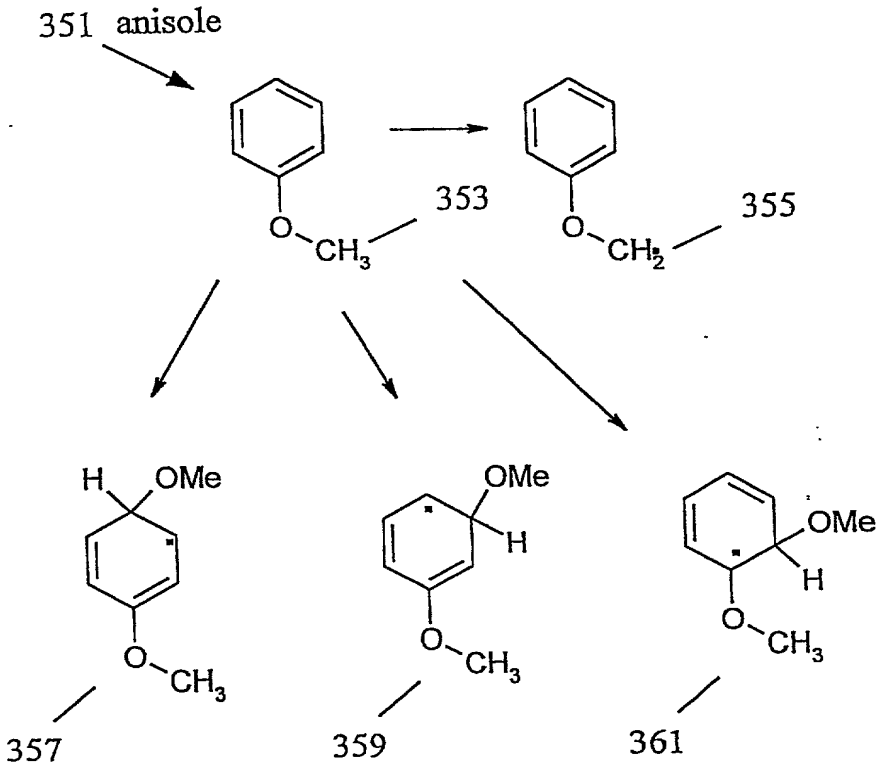


FIGURE 3C

LOVASTATIN		
Regioselectivity/Output Table		
site #	Ea	Lability Bin
1	6.71	labile
2	7.129	labile
3	8.944	moderate
4	9.502	moderate
5	9.806	moderate
6	10.396	moderate
7	10.515	stable
8	10.715	stable
9	10.856	stable
10	10.995	stable
11	11.02	stable
12	11.061	stable
13	11.097	stable
14	11.375	stable
15	11.401	stable
16	11.583	stable
17	11.599	stable
18	11.599	stable
water	10	NA

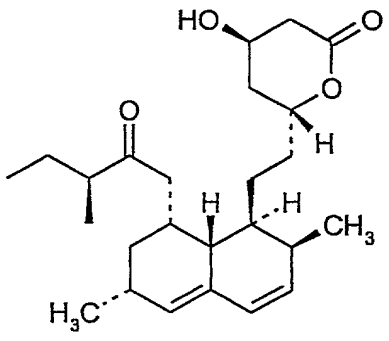


FIGURE 3D

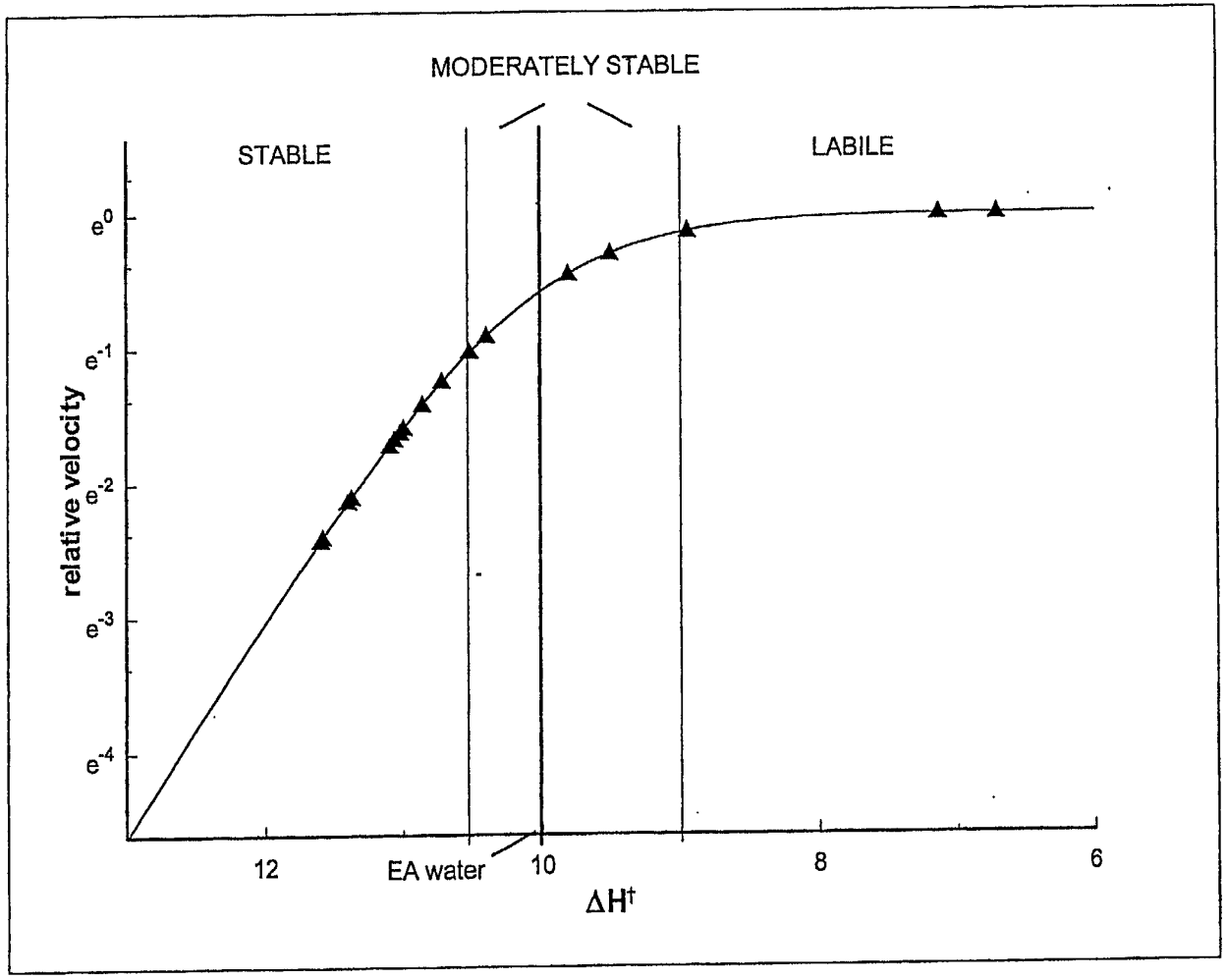


FIGURE 3E

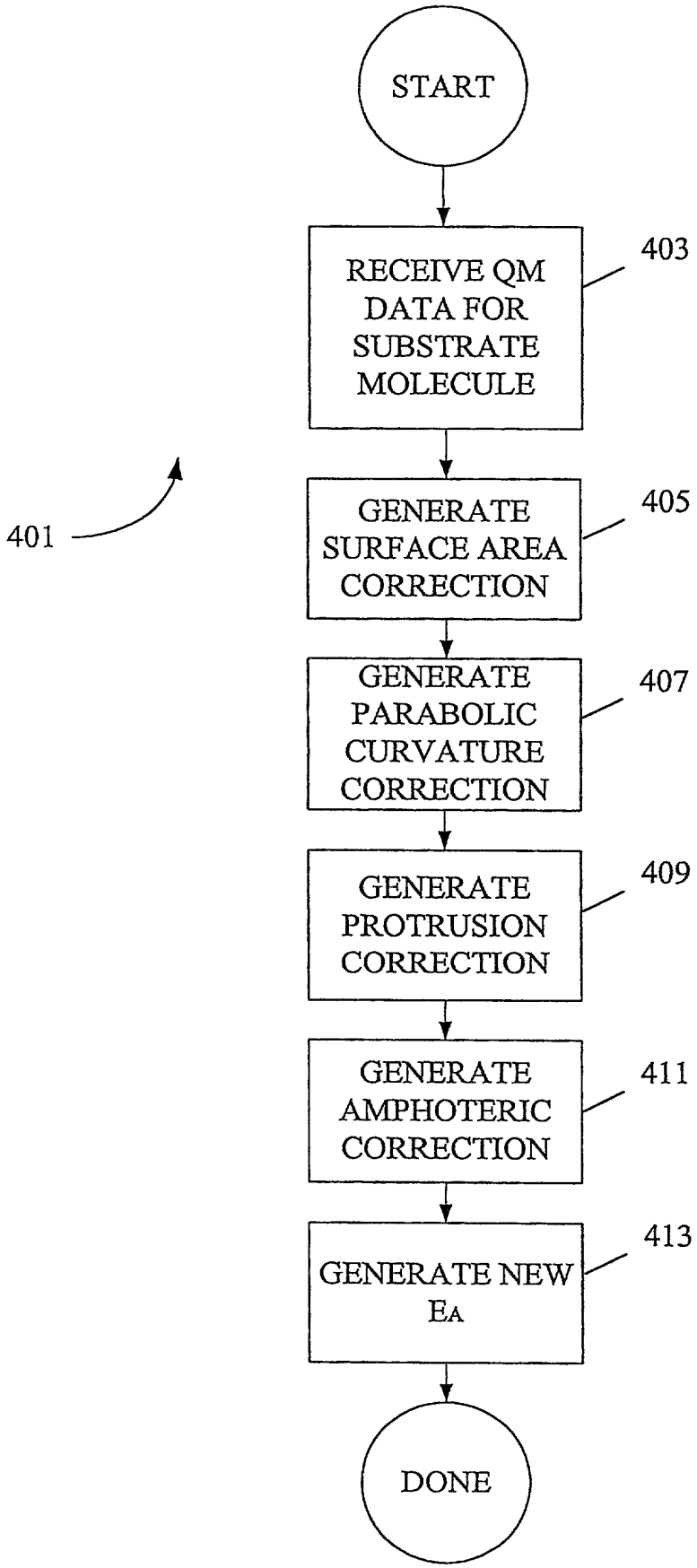
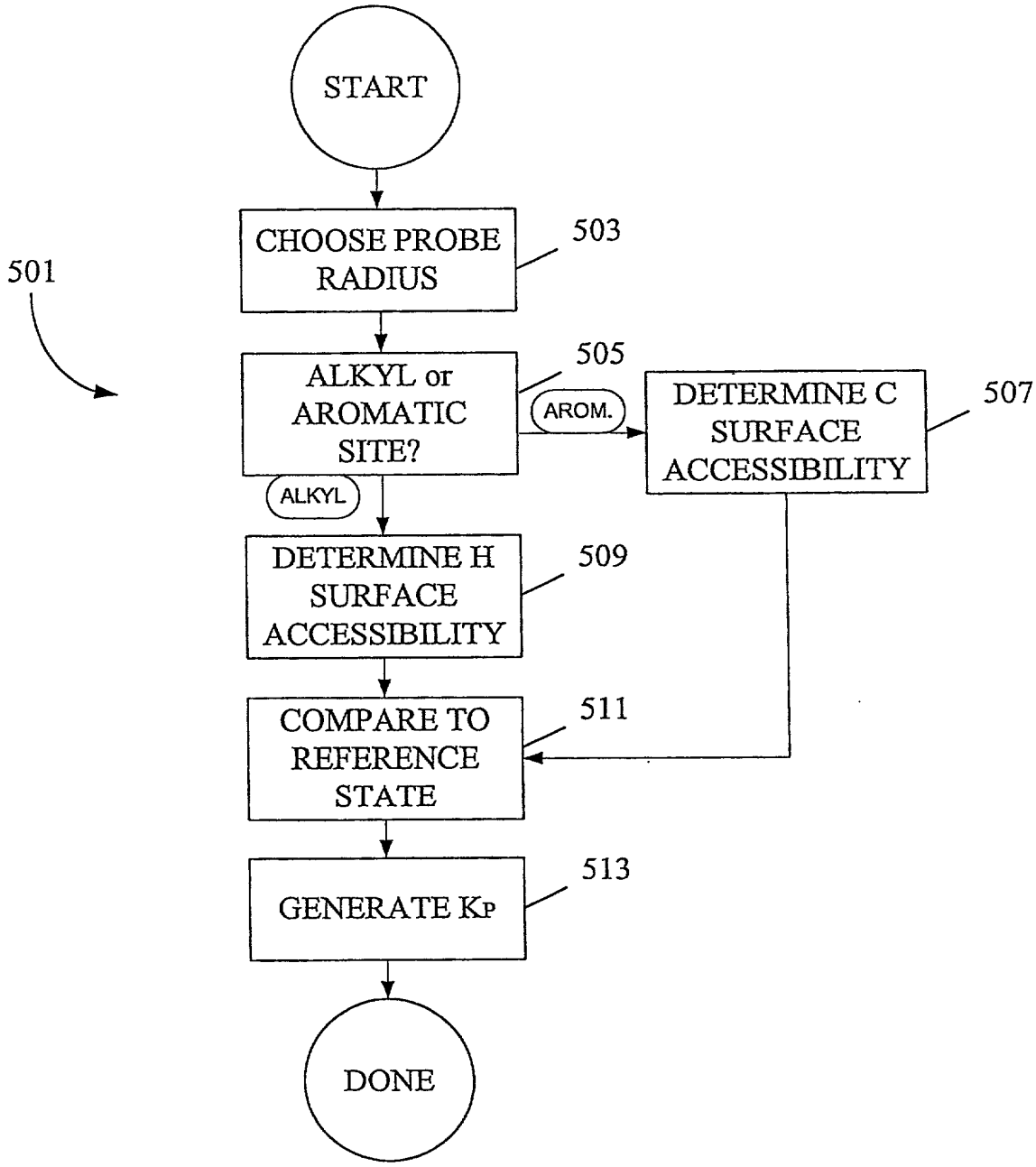

START
RECEIVE QM DATA FOR SUBSTRATE MOLECULE
403
401
GENERATE SURFACE AREA CORRECTION
405
GENERATE PARABOLIC CURVATURE CORRECTION
407
GENERATE PROTRUSION CORRECTION
409
GENERATE AMPHOTERIC CORRECTION
411
GENERATE NEW EA
413
DONE

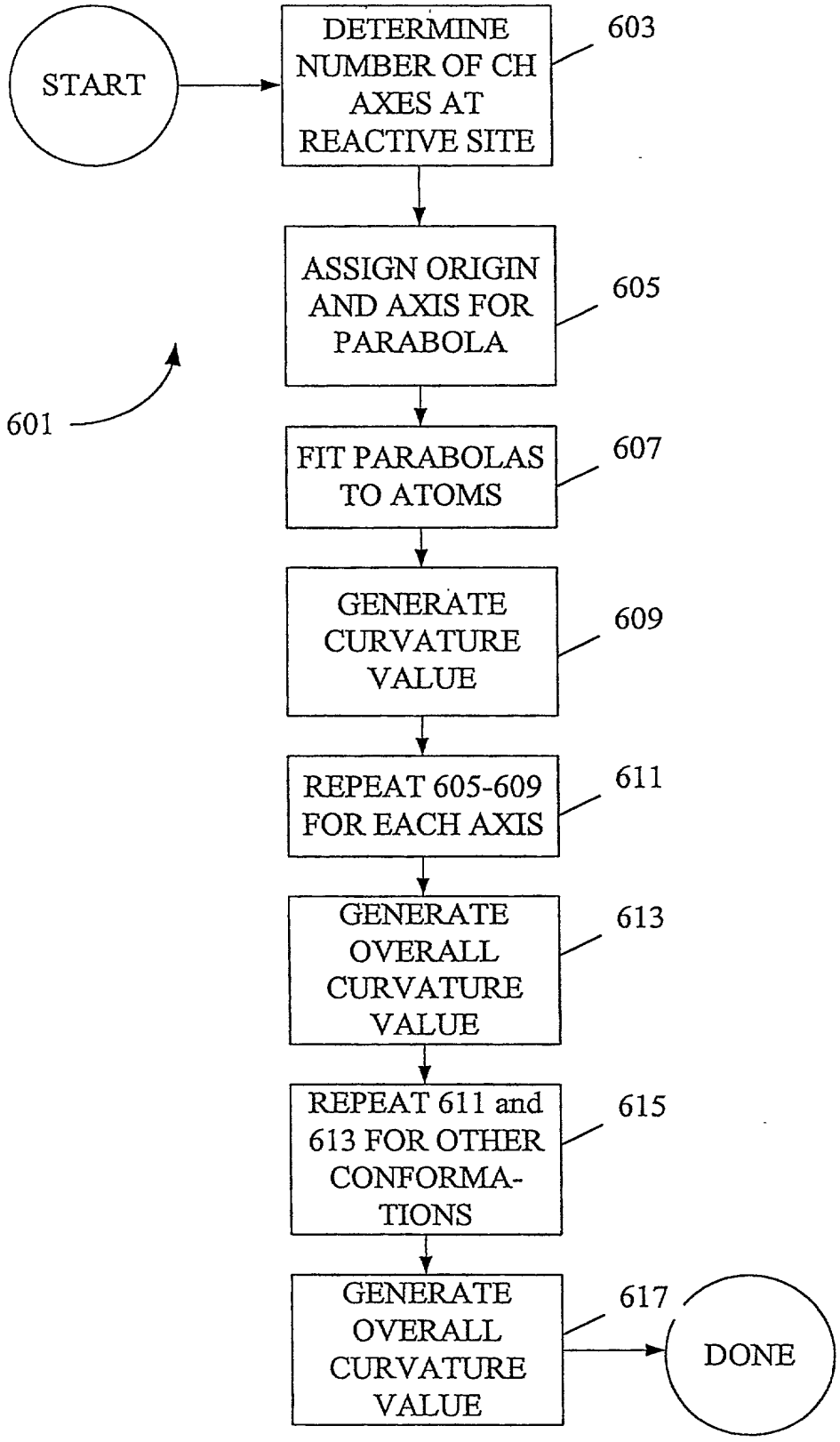
FIGURE 4



SURFACE AREA CORRECTION

$K_{Sa} = X_{Sa} f(S(r))$

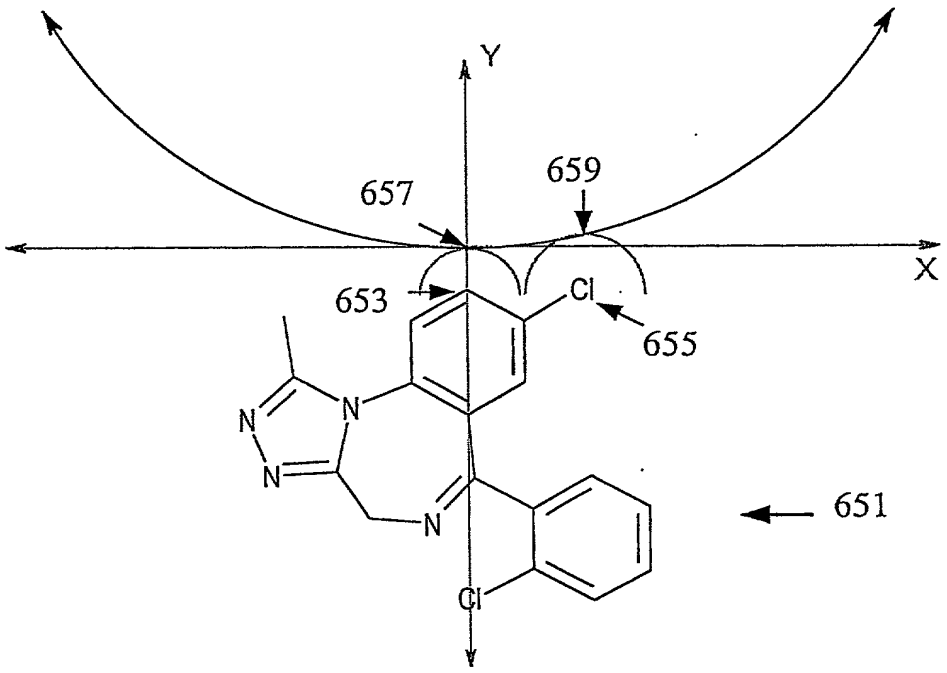
FIGURE 5



PARABOLIC CURVATURE CORRECTION

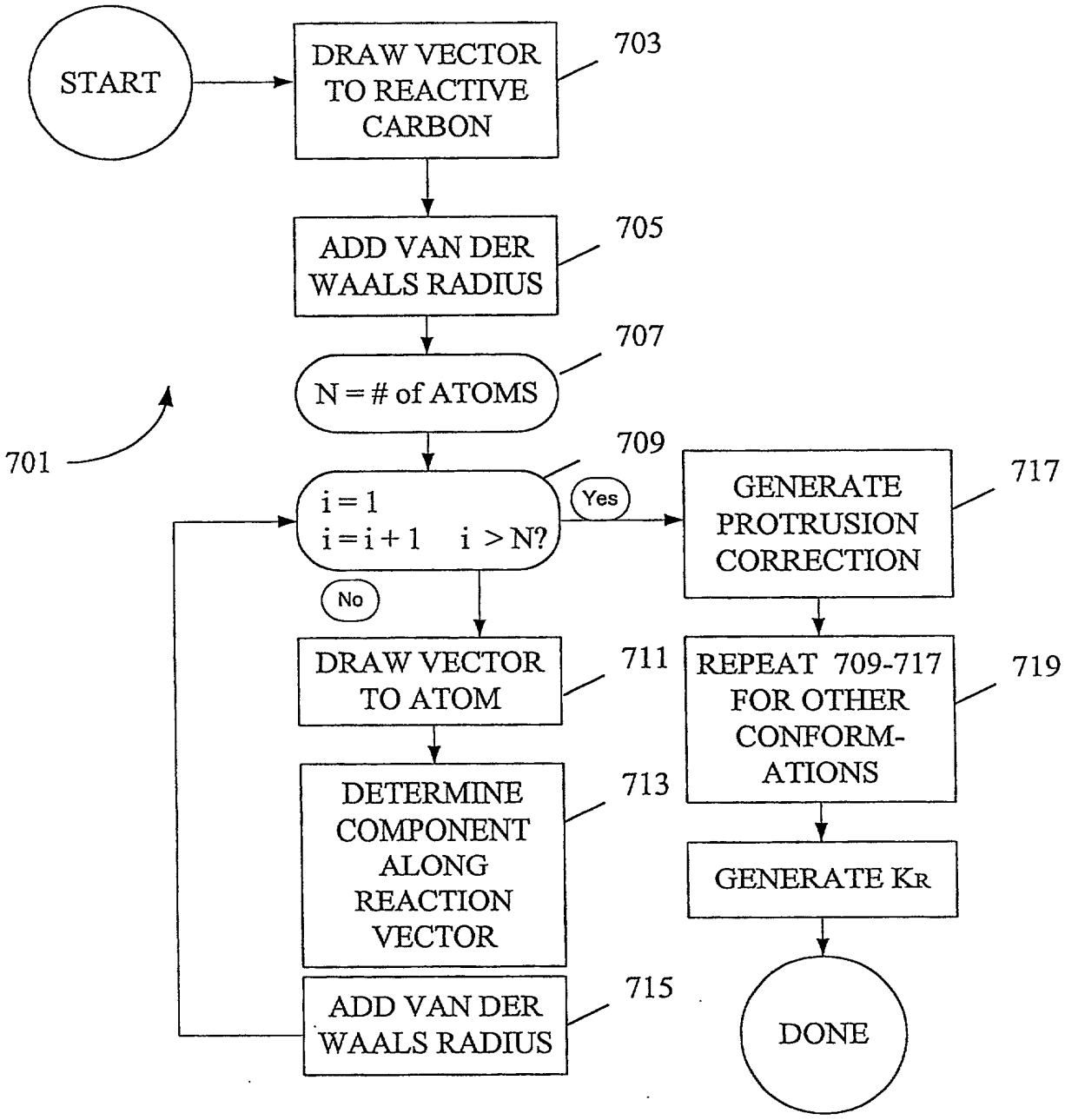
$K_P = X_G P_G + X_S P_S + X_L P_L$

FIGURE 6A



triazolam

FIGURE 6B



PROTRUSION CORRECTION

$K_R = Y_G R_G + Y_S R_S + Y_L R_L$

FIGURE 7A

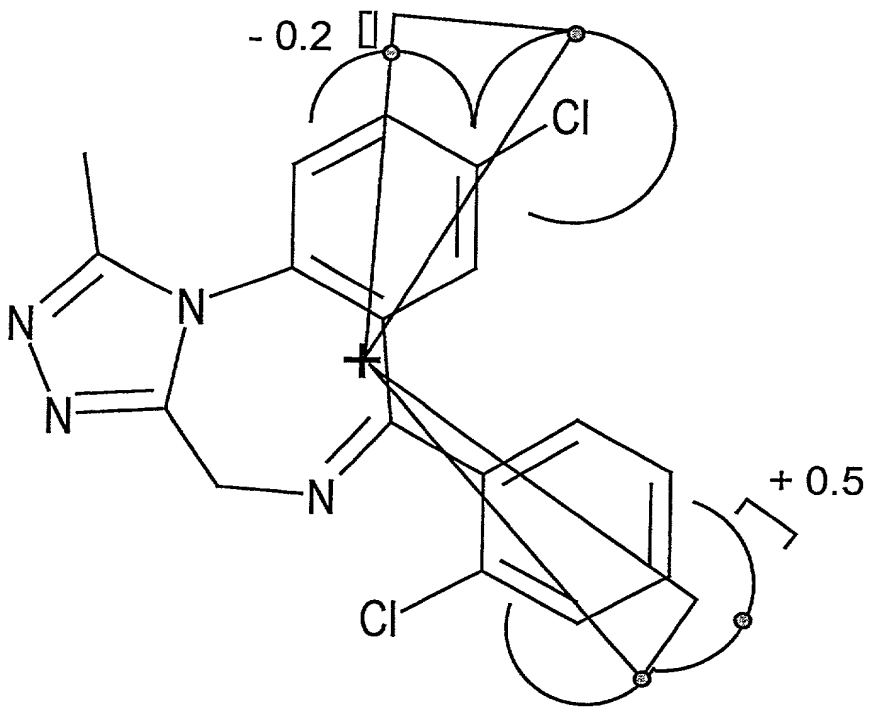
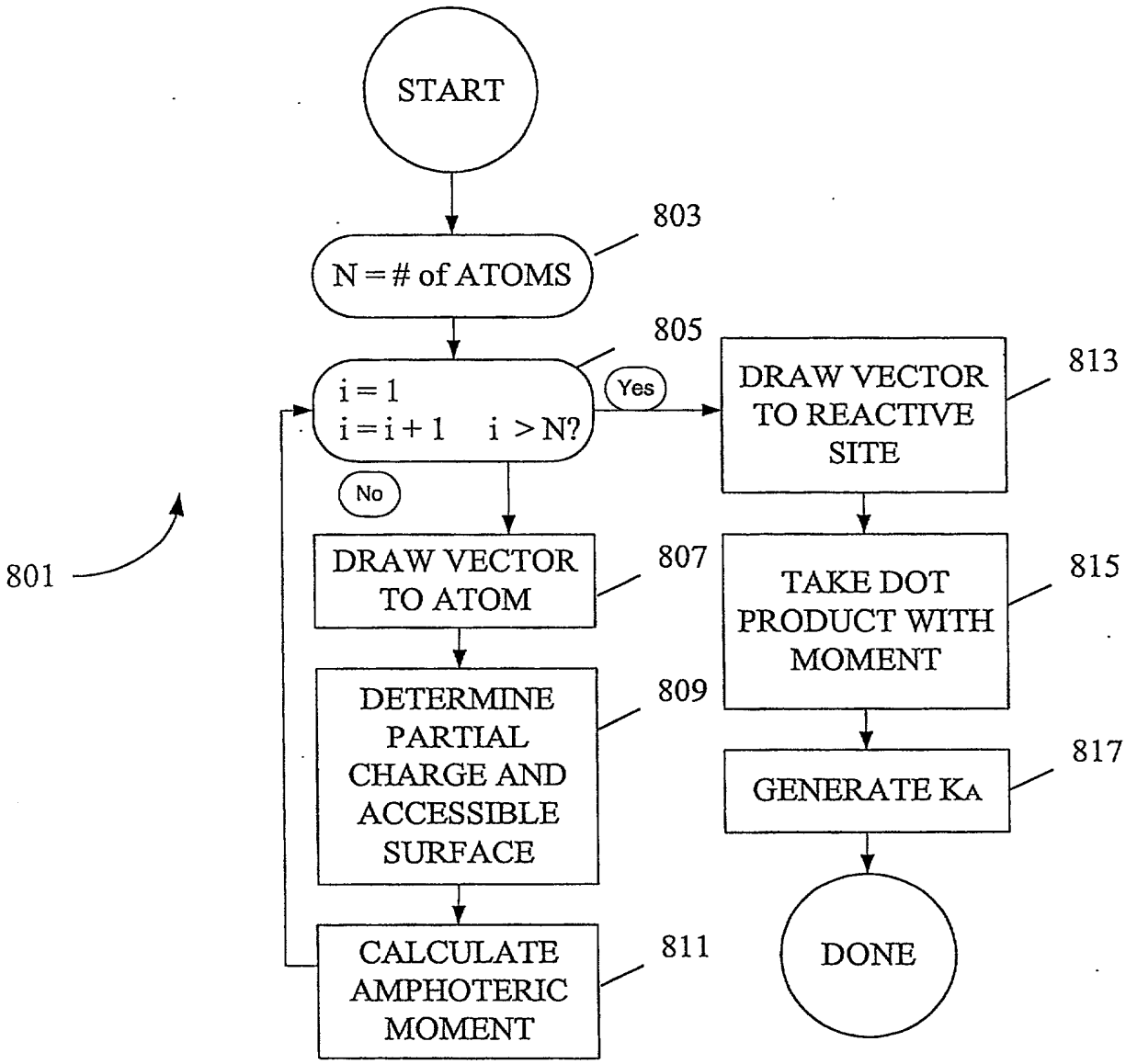


FIGURE 7B



AMPHOTERIC CORRECTION

FIGURE 8

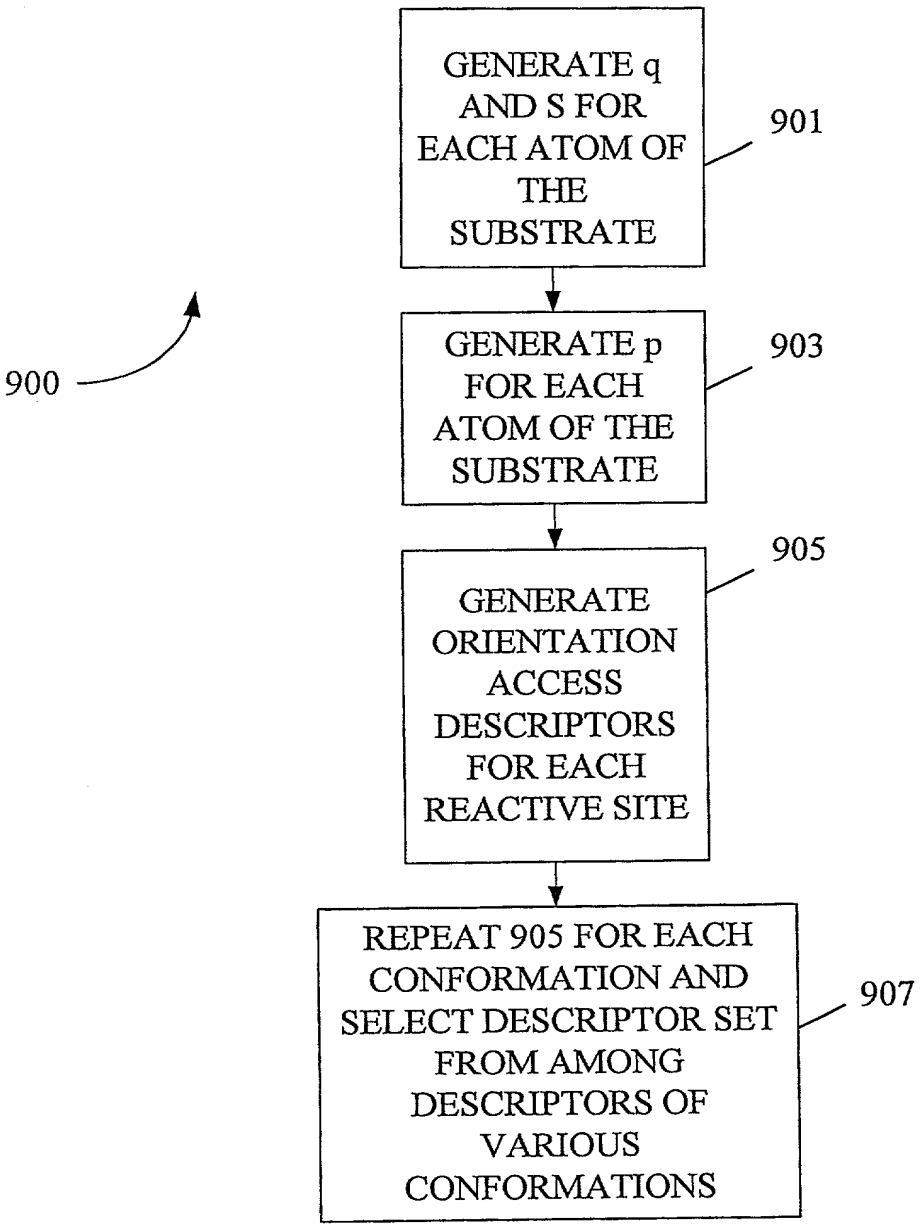

GENERATE q AND S FOR EACH ATOM OF THE SUBSTRATE
901
GENERATE p FOR EACH ATOM OF THE SUBSTRATE
903
GENERATE ORIENTATION ACCESS DESCRIPTORS FOR EACH REACTIVE SITE
905
REPEAT 905 FOR EACH CONFORMATION AND SELECT DESCRIPTOR SET FROM AMONG DESCRIPTORS OF VARIOUS CONFORMATIONS
907
900

FIGURE 9

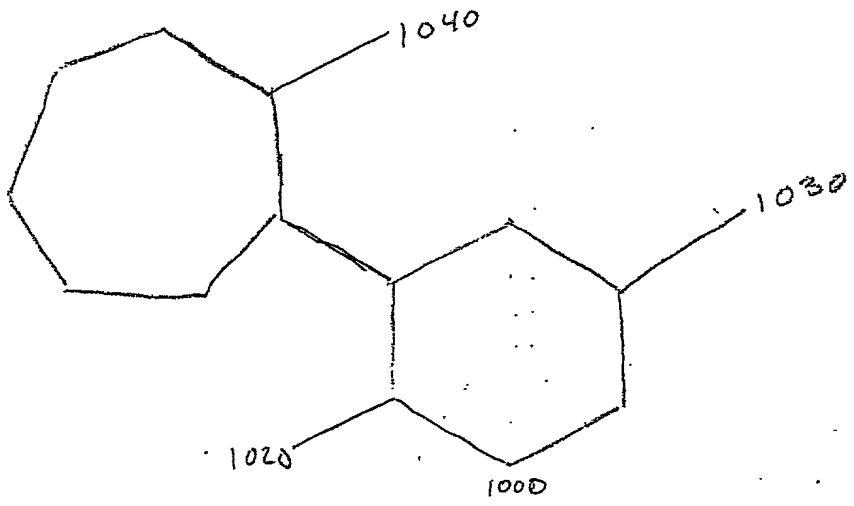


FIG 10

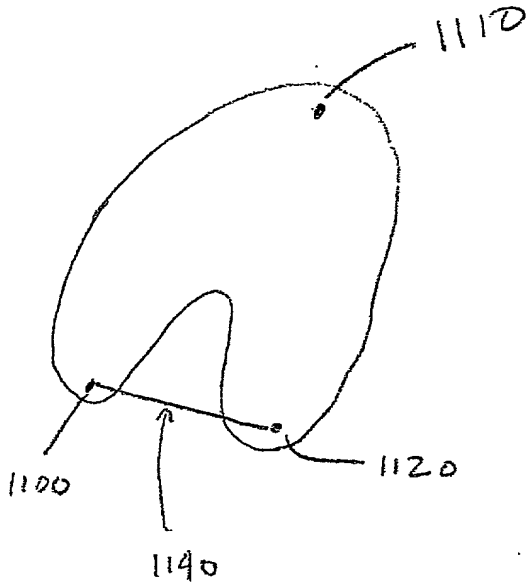


FIG 11

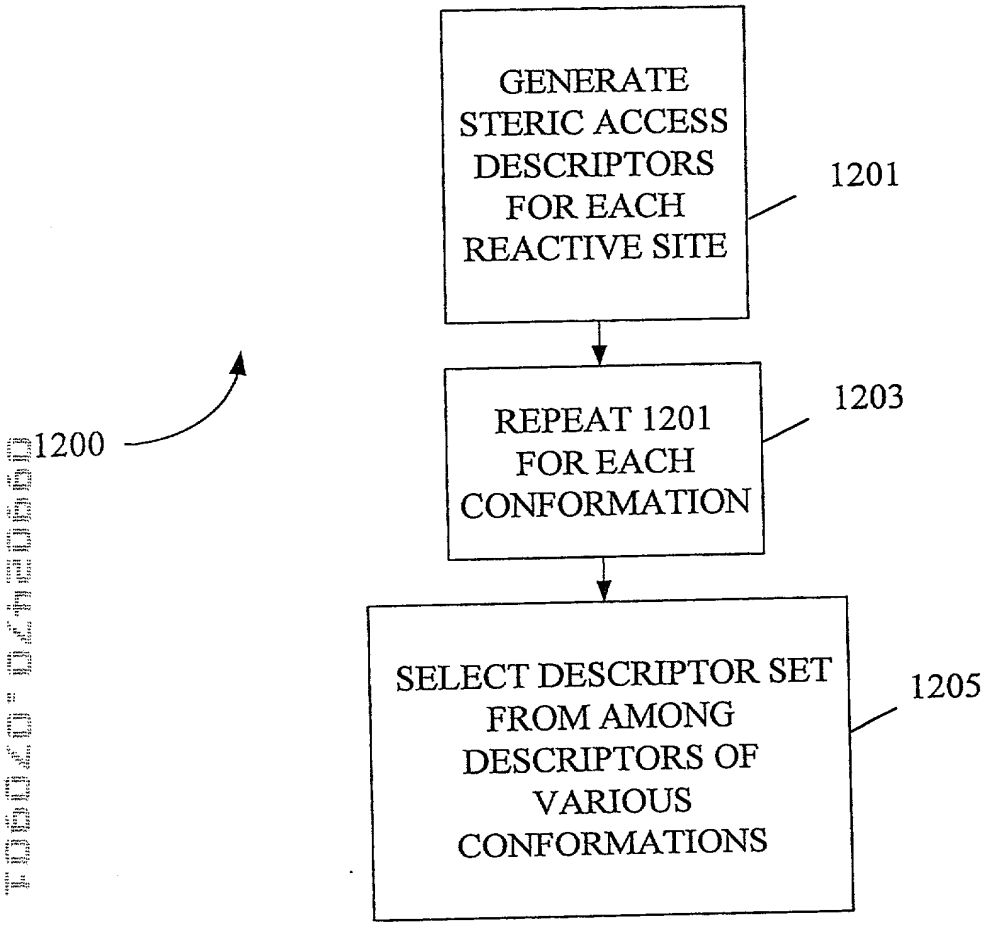

GENERATE STERIC ACCESS DESCRIPTORS FOR EACH REACTIVE SITE
1201
REPEAT 1201 FOR EACH CONFORMATION
1203
SELECT DESCRIPTOR SET FROM AMONG DESCRIPTORS OF VARIOUS CONFORMATIONS
1205
1200

FIGURE 12

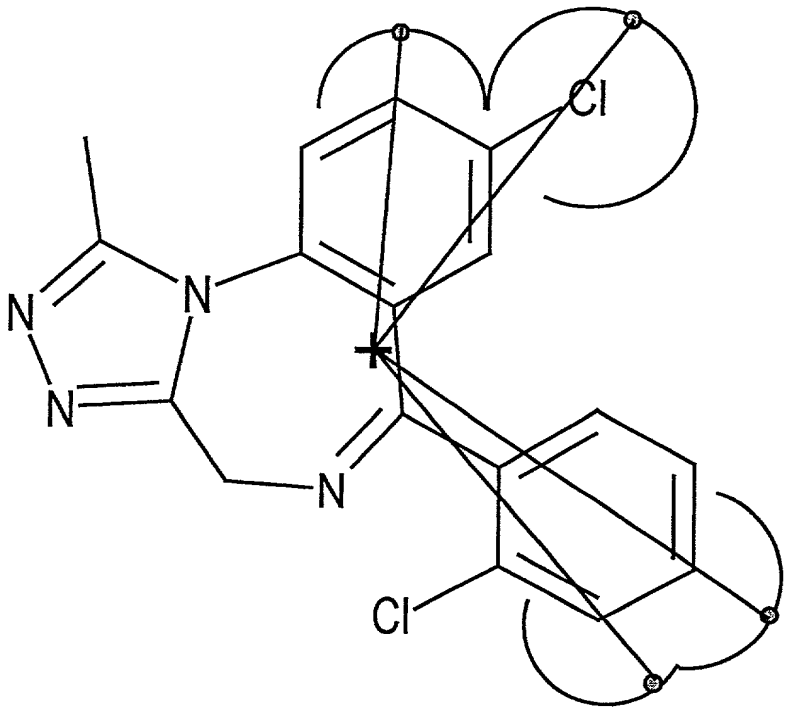


FIGURE 13

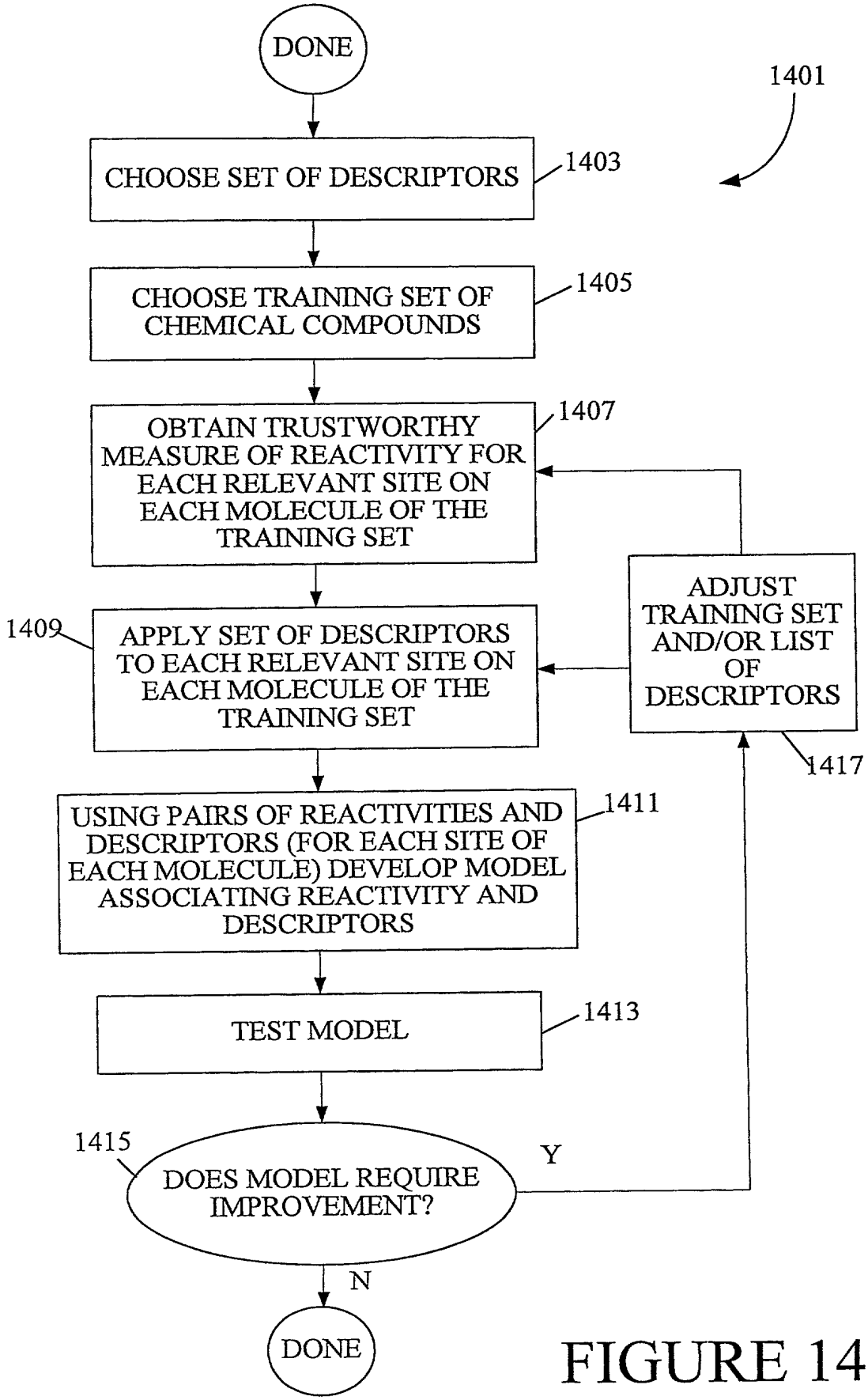
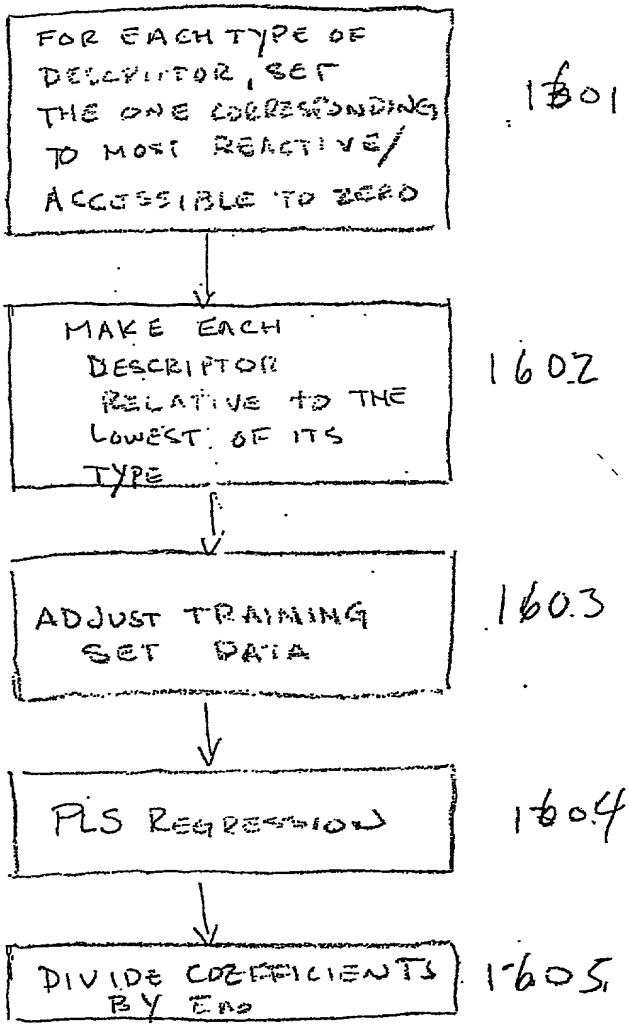

DONE
1401
CHOOSE SET OF DESCRIPTORS
1403
CHOOSE TRAINING SET OF CHEMICAL COMPOUNDS
1405
OBTAIN TRUSTWORTHY MEASURE OF REACTIVITY FOR EACH RELEVANT SITE ON EACH MOLECULE OF THE TRAINING SET
1407
ADJUST TRAINING SET AND/OR LIST OF DESCRIPTORS
1417
1409
APPLY SET OF DESCRIPTORS TO EACH RELEVANT SITE ON EACH MOLECULE OF THE TRAINING SET
USING PAIRS OF REACTIVITIES AND DESCRIPTORS (FOR EACH SITE OF EACH MOLECULE) DEVELOP MODEL ASSOCIATING REACTIVITY AND DESCRIPTORS
1411
TEST MODEL
1413
1415
DOES MODEL REQUIRE IMPROVEMENT?
Y
N
DONE

FIGURE 14

FIGURE 15

16

16A



16B

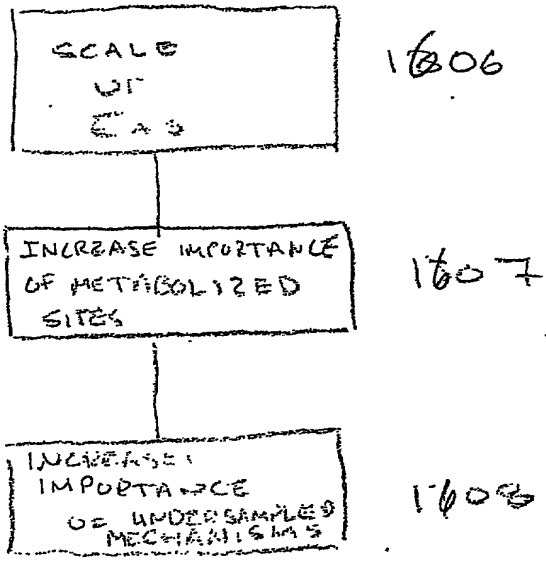


FIG 16

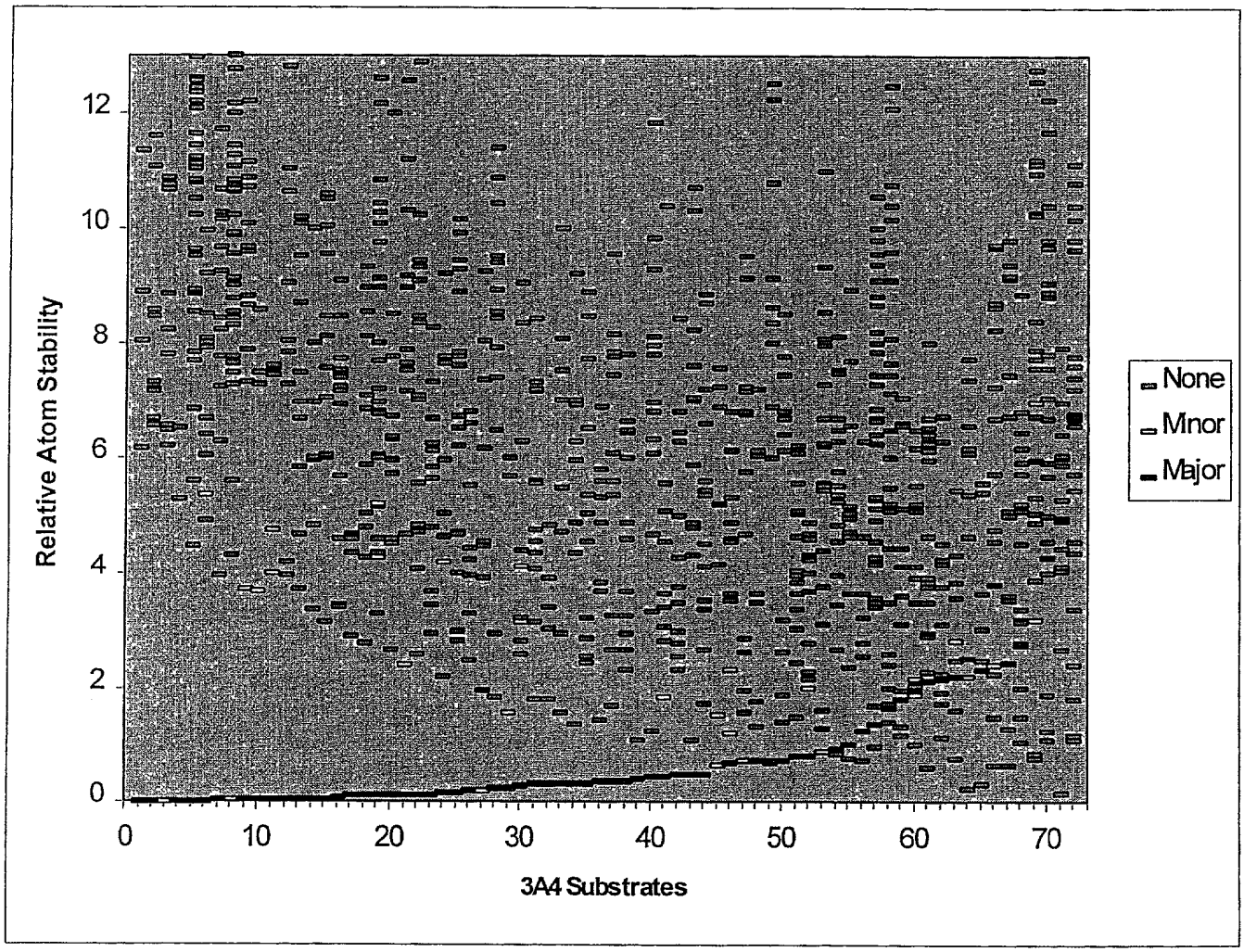

Relative Atom Stability
12
10
8
6
4
2
0
0
10
20
30
40
50
60
70
3A4 Substrates
None
Mnor
Major

FIGURE 17

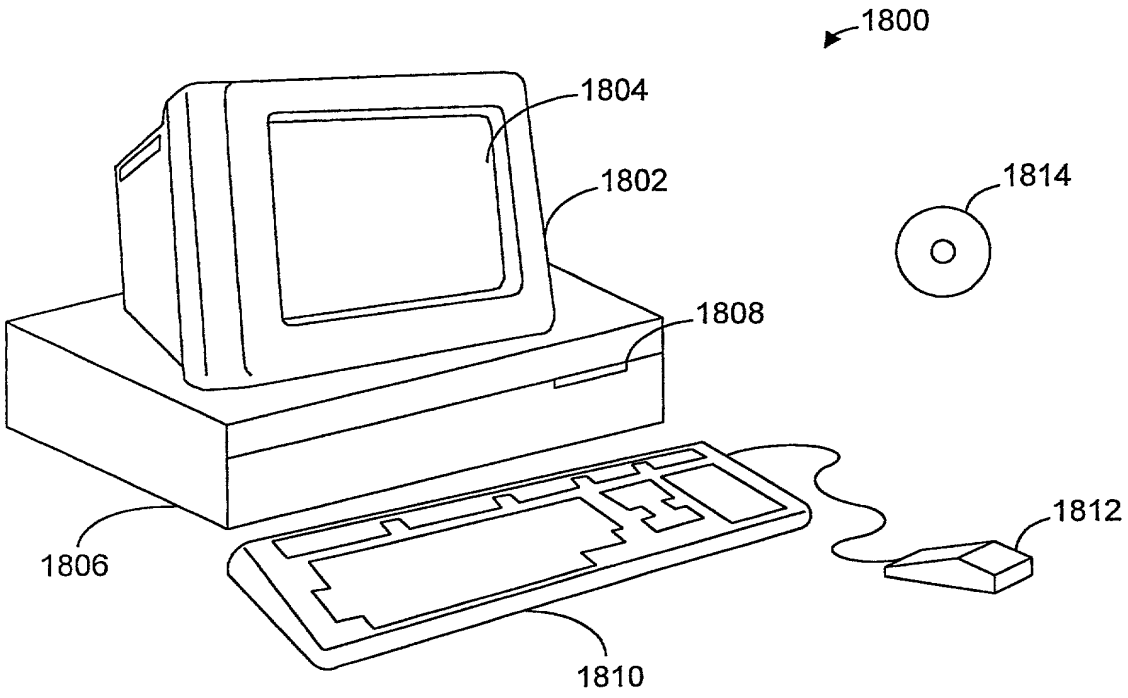


Figure 18A

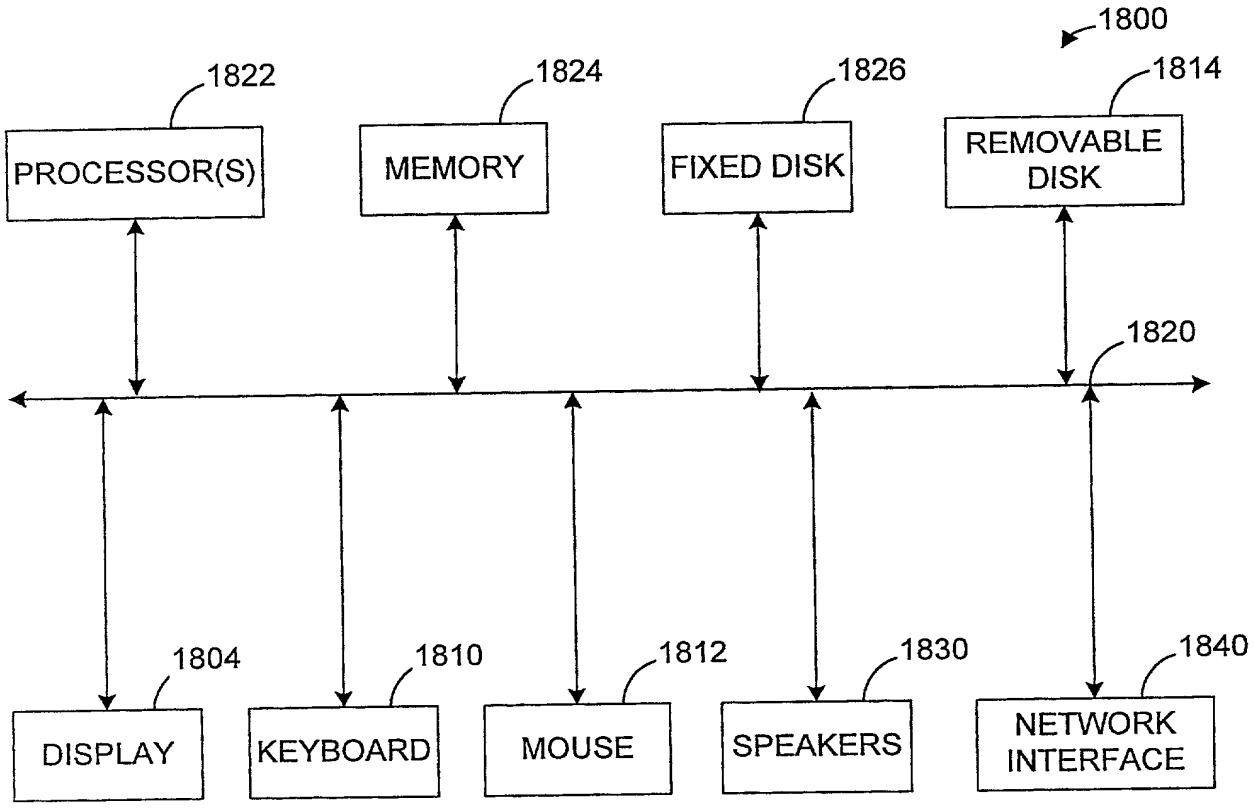


Figure 18B

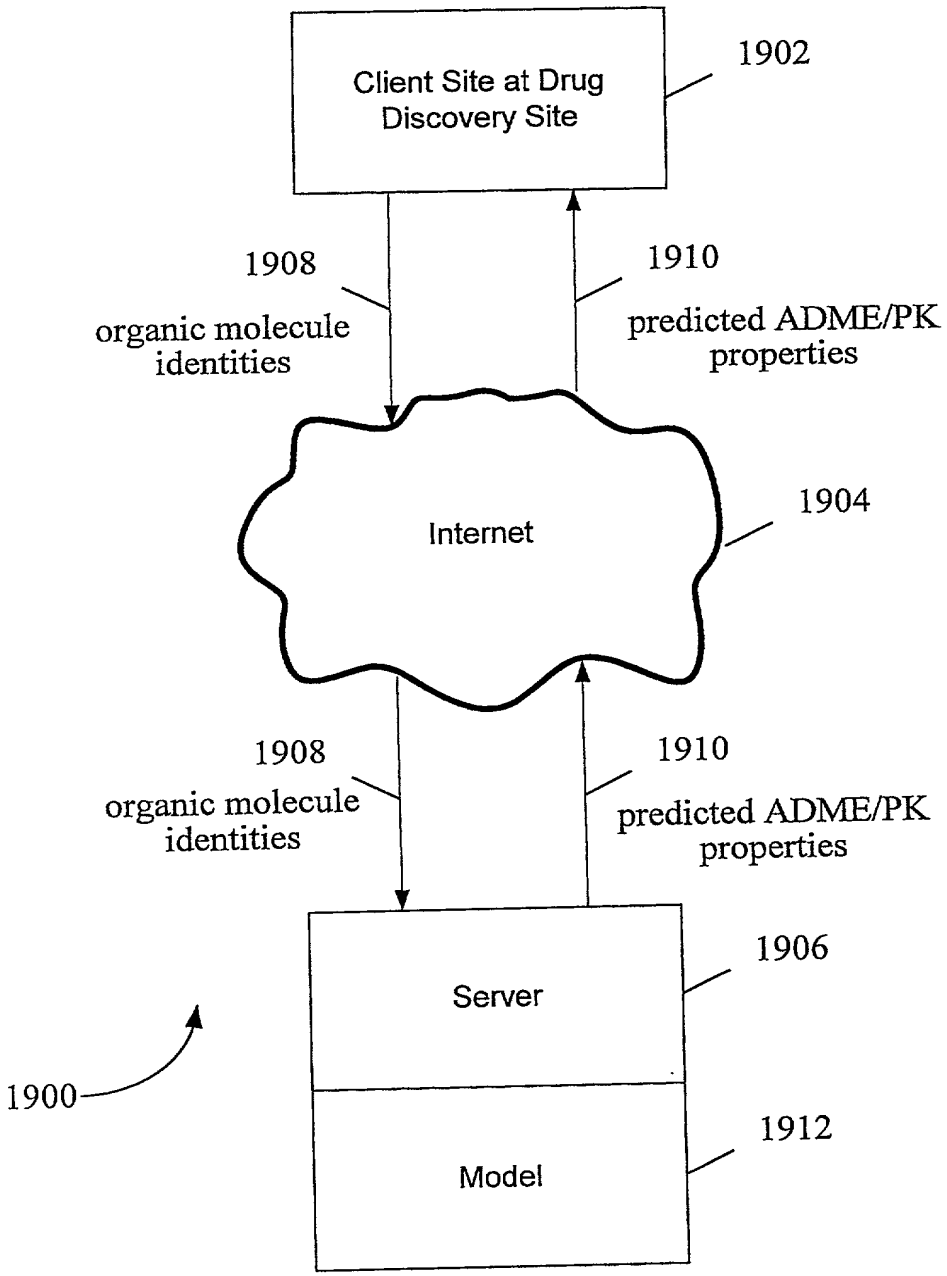

Client Site at Drug Discovery Site
1902
1908
organic molecule identities
1910
predicted ADME/PK properties
Internet
1904
1908
organic molecule identities
1910
predicted ADME/PK properties
Server
1906
1900
Model
1912

FIGURE 19